

January 31, 2002

MEMORANDUM

SUBJECT: **Imazalil.** PC Code: 111901 Case No. 2325 Response to Registrants' Comments concerning the Imazalil Dietary Exposure Document (D263160) and the HED Chemistry Chapter of Reregistration Eligibility Document (D264382). DP Barcode: D267829

FROM: Thurston Morton, Chemist
Reregistration Branch 4
Health Effects Division (7509C)

and

David E. Hrdy, Biologist
Reregistration Branch 4
Health Effects Division (7509C)

THROUGH: Susan V. Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

TO: Dayton Eckerson
Special Review Branch
Special Review and Reregistration Division (7508C)

Action Requested

SRRD requested HED to respond to comments provided by the registrant regarding the HED's dietary exposure and RED chemistry chapter memorandums barcodes D263160 and D264382, respectively.

Executive Summary

This memo is HED's response to the registrant comments on HED's Chemistry RED Chapter and the Dietary Risk Evaluation barcodes D264382 and D263160, respectively. The effective changes to

these two memos, the HED Chemistry RED Chapter and the Dietary Risk Evaluation, were made as indicated in the Agency responses to these comments found herein.

RESIDUE CHEMISTRY

Registrant's comments (#1-11) on the residue chemistry RED chapter for imazalil:

Agency's Response: These changes relating to the use patterns and labels were made as stated in the revised chemistry chapter.

Registrant comment number 12: GLN 860.1380, Page 13 - In the poultry nature of residue study, page 30 under 4.7.6 it states "All samples were analyzed for total radioactivity within one month of sampling. Extraction of samples for partition and metabolite profiling was performed within 3 months of sampling." Therefore, 6 months reported by EPA is incorrect.

Agency's Response: The sentence in the Chemistry Chapter reads "...completed within six months...". Therefore, per OPPTS GLN 860.1380 no storage stability data would be required. The Agency is correct in stating the samples were analyzed **within** six months.

Registrant comment number 13: GLN 860.1480, Page 14 end paragraph 2 - Add a similar statement for hogs and horses (fat) as is made for poultry, since there is no reasonable expectation of finite residues under CFR 180.6 (a)(3) per Table C, page 25.

Agency's Response to comment: The Agency agrees with this statement and has amended the Chemistry RED chapter from HED to reflect this agreement.

Registrant comment number 14: Editorial under subheading *Poultry* - This determination is based on a review of a poultry feeding **study**.

Registrant comment number 15: Footnote table B, Page 18 - Under footnote 2, eliminate reference to 44.6% formulation for post-harvest application per Remark 6 above.

Registrant comment number 16: Footnote to Table B, Page 19 - Under footnote 15, eliminate "and poultry" since no poultry tolerances are required per CFR 180.6(a)(3).

US EPA Response to comments 14 through 16: These corrections have been made as per comments. **However, the issue of poultry layer house fumigation is still unresolved and a poultry/egg study is required reflecting the application of imazalil gas in a layer house scenario (see 773-EUP-R, memo of 8/12/85, A. Reiter and S. Hummel).**

Registrant comment number 17: We request the Agency acknowledge that the tolerances for wheat and barley commodities legalize analytical or other artifacts, and do not represent imazalil *per se* for risk assessment purposes.

US EPA Response to comments: Since there is an imazalil use on wheat commodities and there are data available from USDA's PDP sample program with residues reported above the limit of detection then it is Agency policy to include these detectable residues from USDA's Pesticide Database Program in our dietary exposure assessment.

Registrant comment number 18: Tolerances under 180.413(a), Page 22, paragraph 2 - Cattle dietary burdens based on a diet of predominantly apple pomace are given at Page 14 in Reference 1. Apple registrations will not be supported, as noted by EPA. The dietary burden without apple pomace is listed as 6.8 mg/kg (ppm). At Pages 7-8 in Reference 2, the dietary burdens for dairy cattle and beef cattle are calculated as 6.7 and 4.7 ppm in the Tables, but the beef cattle dietary burden is reported as 6.1 ppm in the text. The numbers are inconsistent.

US EPA Response to comments: The dietary burden tables and the reported burdens have been revised for consistency. The recommendations found in the registrant's comment number 18 do not follow current OPPTS guidance.

Registrant comment number 19: Tolerances needed 180.413(b), Page 23 - HED recommends tolerances of 0.2 ppm in kidney of cattle, goats, ~~hog~~, horses and sheep. Table C lists hog tolerances as revoked per 180.6(a)(3), therefore, this should apply to hogs, kidney as well.

US EPA Response to comments: The Agency agrees and has amended the HED Imazalil Chemistry RED Chapter to reflect the 180.6(a)(3) for hogs, kidney as well.

Registrant comment number 20: Pending Tolerance Petitions, Page 24 – 1) and **revised** PP#4F3096, for the establishment of a tolerance on pear at 10 ppm. 2) **add pp#7F3530** for tolerances on melons (excluding watermelon) by post-harvest application and sweet corn by seed treatment

US EPA Response to comments: These revisions to HED Imazalil RED Chemistry Chapter have been made according to the registrants comment number 20.

General Comments By the Registrant concerning the Dietary Exposure Assessment Memorandum dated March 23, 2000:

Registrant: *General Comment: When citrus fruits and bananas/plantains are treated post-harvest at registered rates, measurable residues will be found on whole fruit and in the edible portion, regardless of storage time. Therefore, when PDP data are available, the percent of samples testing positive for imazalil is a direct measure of the percent crop treated (%CT). Estimates from the PDP should supercede %CT estimates from proprietary surveys or from the registrants.*

US EPA Response to comments: Agency guidance as per HED SOP 99_6, M. Stasikowski, 8/20/99) advises that for acute assessments for a tier 3 that the maximum estimated percent crop (BEAD, J. Alsadek, January 19, 2000) treated should be used. Although a treated sample may not result in residue in residues reported greater than the LOD after analysis, the residues may exist which are at/or below the level of detection (LOD).

Registrant: *We believe that the Agency estimate of 48-52% (banana/plantain) crop treated is in error. The 1994 and 1995 PDP data set should be used “as is” or, the data can be backfilled with zeroes to approximate 25% CT.*

US EPA Response to comments Agency guidance as per HED SOP 99_6, M. Stasikowski, 8/20/99) advises that for acute assessments for a tier 3 that the maximum estimated percent crop (BEAD, J. Alsadek, January 19, 2000) treated should be used. Although a treated sample may not result in residue in residues reported greater than the LOD after analysis, the residues may exist which are at/or below the level of detection (LOD).

Registrant: *What is the basis for N=12? On page 7; What is the “N” and its basis?*

US EPA Response to comments: The N= 12 is the number of units or single bananas that are in a single sample/analysis. The basis of N is described in the following quoted from an internal draft reviewer’s aid document for use in decomposition of commodities that are considered eaten on a unit basis.

“To explain the correction for refuse by example, the weight in the Nutrient Database for the consumed portion of a medium apple is 138 g. This assumes 8% percent refuse for core and stem. The PDP 5 lb (2270 g) samples include the whole apple, including core and stem. [Note that PDP does remove the core and stem from apples prior to analysis, but only after the 5 lb sample has been weighed.] Therefore the corrected weight in the table is $138 \text{ g} / (100\% - 8\% \text{ refuse}) = 150 \text{ g}$. The value of “n” is calculated by dividing this result into 5 lbs (2270 g), so that $2270 / 150 = 15.1$, rounded to 15.”

Registrant: *At Page 4, Ref. 2, an average residue value of 0.013 ppm is calculated for bananas and plantains. We did not have sufficient information to confirm the calculation. Please provide the residue file and a description of how it was created*

US EPA Response to comments: The number used in the dietary assessment for both acute and chronic analysis is from a calculation which included the $\frac{1}{2}$ LOD value when the sample was considered treated but not detected upon analysis. This calculation resulted in an average of 0.014 ppm. The sensitivity analysis for the cancer dietary exposure analysis used an average of 0.008 ppm when zeroes were inserted in place of the $\frac{1}{2}$ LOD values. The residue values

used can be seen as an attachment in the most recent dietary exposure analysis memorandum (T. Morton, D280449, 1/24/02).

Registrant concerning Barley and Wheat: *At page 4 (barley) and Page 6 (wheat) in Reference 2, the Agency said it translated wheat data from the PDP, in which 21 of 1,483 samples tested positive (1%). In the next sentences, the Agency used a “conservative default of 100% [CT]”. The 2 statements are at variance with each other.*

US EPA Response to comments: The Agency agrees with the registrant. The initial dietary assessment did make the assumption that the non-detects are really zeroes and the editorial correction was made. The calculation of the anticipated residue for the sensitivity analysis resulted in 0.000176 ppm compared to the 100 %CT calculated anticipated residue of 0.00313 ppm. However, BEAD has now reported % crop treated information for wheat and barley. This % crop treated information will be used in the revised dietary exposure analyses. BEAD provided an estimate of 4 % CT for the average and a high end estimate of 5 % CT for wheat from seed treatment (only registered use). BEAD provided an estimate of 1 % CT for the average and a high end estimate of 2 % CT for barley from seed treatment

Registrant’s Comments: *CITRUS Fresh oranges:*

Use of the PDP %CT at Page 4 (Ref. 2), Allender decomposition, and backfilling the residue file with zeros appears to be correct with the parameters listed at Page 28 in Reference 2. Again, clarification is needed:

What is the “N” and its basis?

US EPA Response to comments: Please refer to the Agency’s response to the same issue in bananas beginning on page 4 of this document.

Registrant’s comments: *Based on the PDP, 56% of the fresh crop is treated (see Page 4, Ref. 2). In the Table at Page 9 (Ref. 2), 18-22% of fresh oranges are reported as treated and 2-6% of the entire crop as treated. The numbers are not consistent.*

US EPA Response to comments: PDP is considered by OPP to be a preferred source of information especially where there is more likelihood of a post harvest application. The sources of information BEAD uses to estimate their %CT normally do not capture post harvest treatment information. Therefore, the Agency policy is to use PDP percent crop treated information whenever PDP data are available.

Registrant’s Comments: *Processed Oranges (Juice)*

- *At Page 5, Ref. 2, EPA states that “20% CT was employed for purposes of imazalil use on oranges (for juice concentrate, juice and fresh oranges).”*

Is “fresh oranges” correct?

US EPA Response to comments: Yes, although it is better to say orange-juice, uncooked because this is the exact entry for fresh orange juice in DEEM, the dietary model used to estimate the overall exposure. However, the revised dietary exposure analyses used 6 % CT for orange juice/juice concentrate in the revised acute analysis and 4 % CT for the revised chronic analyses.

Registrant’s Comment: *In the Table at Page 9, Ref. 2, the processed oranges are reported as 2-6% of the crop not 20%. Based on the PDP, only 3% of the samples of orange juice concentrate resulted in detectable residue (see Page 4, Ref). The PDP confirms the 2-6% estimate of total crop treated.*

US EPA Response to comments: The revised dietary exposure analyses used 6 % CT for orange juice/juice concentrate in the acute analysis and 4 % CT for the chronic analyses.

Registrant’s Comment: *At Page 4, Ref. 2, EPA states that “Orange juice concentrate was translated to orange juice per se through back calculation explained herein”
No explanation is given.*

US EPA Response to comments: The revised dietary exposure analyses contains a table of modified processing factors for citrus juice and juice concentrate when PDP data for juice is available. These modified processing factors maintain the DEEM default ratio for juice/juice concentrate.

Registrant’s comments: *From the text in this section, and the list of residue fields given at Page 39, Ref. 2, we cannot determine what residue values were used in the assessments. We therefore cannot concur, identify errors or recommend refinements. Additional information is needed. Please provide the residue file and a description of how it was created.*

US EPA Response to comments: The residue values used can be seen as an attachment in the most recent dietary exposure analysis memorandum (T. Morton, D280449, 1/24/02).

Registrant’s comments: *Tangerines, Limes, and Lemons*
From the text in these sections (pages 5-6, Ref.2), and the list of residue files given at Page 39 Ref. 2, we cannot concur, identify errors, or recommend refinements. Was the orange single serving residue distribution used for single servings of these commodities? Additional Information is needed. Please provide the residue file and a description of how it was created.

US EPA Response to comments: Yes, orange data were used to surrogate for tangerines, limes and lemons and adjusted where necessary due to differences in % crop treated. The residue values used can be seen as an attachment in the most recent dietary exposure analysis memorandum (T. Morton, D280449, 1/24/02).

Registrant's comments: Grapefruit

- *Grapefruit (peeled fruit) was identified as a risk driver at Page 11, Reference 2. and at Page 17, Ref. 3. From the text at Page 5, Ref. 2, and the list of residue files given at Page 39, Ref. 2, we cannot determine what residue values were used in the assessments. We therefore cannot concur, identify errors, or recommend refinements.*

We note that single serving grapefruits are a risk driver and PDP data are available. Were PDP data used? If not, why not? Was the orange single serving residue distribution used for grapefruit?

US EPA Response to comments: Grapefruit was a risk driver and PDP data were translated from oranges to grapefruit because there are more recent data. The residue values used can be seen as an attachment in the most recent dietary exposure analysis memorandum (T. Morton, D280449, 1/24/02).

Registrant's comments: Additional information is needed. Please provide the residue file and a description of how it was created.

US EPA Response to comments: The residue values used can be seen as an attachment in the most recent dietary exposure analysis memorandum (T. Morton, D280449, 1/24/02).

Registrant's comments: Milk/Milk/Poultry/Eggs At page 7, Ref. 2 the EPA reports no detectable residues in 474 PDP milk samples (LOD = 0.004 ppm). The Agency assumed ½ LOD (0.002 ppm) and (implicitly) 100% of all milk containing residues. At page 39, Ref. 2, no residue file is listed for milk. Was milk included in the analysis?

US EPA Response to comments: Milk was not included in the assessment because of the above statement “no detectable residues in 474 PDP milk samples (LOD = 0.004 ppm).”

Registrant's comments: The text at Page 7, Ref. 2, refers to Ref. 1, which specifies using the total toxic residue as calculated from the dairy cow metabolism study. The TTR would be adjusted for the difference in dosing in the metabolism study as compared to the calculated worst case dietary burden.

US EPA Response to comments: That is correct, the total radioactive residue (TRR) was adjusted for the difference in the dosing in the metabolism study as compared to the calculated worst case dietary burden.

Registrant's comments: At Page 8, Ref. 2, the Agency: "used the following point estimates to conservatively approximate the residue of imazalil found in milk and meat. Meat, milk and fat estimated residues in this assessment are 0.001 ppm while liver and kidney estimated residues are 0.04 ppm."

The above three statements are contradictory. What residue values were used in the dietary assessment and what was the rationale?

US EPA Response to comments: Milk was not included in the assessment. Livestock tissue anticipated residues were calculated using the imazalil residues from the ruminant feeding study and adjusted using a ratio obtained from the ruminant nature of the residue study to account for all of the residues of concern (2,4-dichlorophenyl metabolites).

cc : Chem F, Chron F, Morton, Hrdy

RDI: SVH:1/31/02

TM, Thurston Morton, Rm. 816D CM2, 305-6691, mail code 7509C